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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,259	09/12/2001	Nestor Annibali	52071.00004	1187

7590 07/22/2005

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EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,259	ANNIBALI, NESTOR	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *6-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 24* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed May 4, 2005. Amendments were made to the claims.

Claims 1-24 are pending in the instant application. Claims 6-23 are withdrawn as being drawn to a non-elected invention. Claims 1-5 and 24 are under consideration in the instant application. Any rejection of record in the previous Office Action, mailed January 4, 2005, that is not addressed in this action has been withdrawn.

Applicant's arguments with respect to claims 1-3, 5 and 24 have been considered but are moot in view of the new ground(s) of rejection.

Priority

Receipt is acknowledged of a translation for papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The substitute specification filed May 4, 2005 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Brierley *et al.* (US 5,324,639; see entire document; henceforth Brierley).

Brierley teaches the construction of a methylotrophic yeast strain of the genus *Pichia* (*P. pastoris*), wherein the yeast comprises an expression construct for the recombinant production of insulin-like growth factor-1 (IGF-1) (see for example the Abstract and column 3, lines 32-62). IGF-1 is a polypeptide that shares biological activity with insulin (see for example column 1, lines 33-41). Thus, by definition, IGF-1 represents an "analog" for a human insulin precursor because IGF-1 is a molecule "showing the same biological activity as insulin, as measured by tests known by those skilled in the art" (see for example page 23 of the instant substitute specification). A specific construct taught by Brierley comprises a promoter for a methanol responsive gene, operably linked to the *S. cerevisiae* α-mating factor (AMF) export signal as fused to IGF-1, and further operably linked to a transcriptional terminator (see for example column 4, lines 13-30). The constructs can also comprise a selectable marker gene such as *HIS4* or *ARG4* (see for example column 7, lines 39-54). Finally, Brierley teaches that one or more (i.e., two) of these constructs can be integrated into the genome of the yeast at the same or different loci (see for example column 8, lines 5-32), and the skilled artisan would clearly recognize the need to use two constructs having two different selectable markers when selecting an integrant having multiple integrated copies (otherwise, there would be no guarantee that two specific integration events had occurred). As such, Brierley anticipates the invention as indicated in the above claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raymond (US 5,955,349; see entire document; henceforth Raymond).

Raymond teaches the construction of a methylotrophic yeast species, specifically *Pichia methanolica*, wherein the yeast is genetically modified to express a heterologous polypeptide (see for example the Abstract and column 1, lines 52-61). The modification occurs via a DNA construct, which itself comprises a promoter element (such as the alcohol oxidase (*AOX1*) promoter), the heterologous peptide of interest, a terminator sequence and a selectable marker (such as *ADE2*) (see for example column 1, line 52 to column 2, line 10). Raymond further teaches that the yeast strains can be "integrative transformants" where the construct is integrated into the genomic DNA of the host cell for the production of a preferred type of yeast strain with a profound growth advantage (see for example column 3, lines 9-11 and column 11, lines 31-56). These strains can be used for the production of polypeptides, including human polypeptides (see for example column 4, lines 2-4), more specifically a polypeptide such as insulin (see for example column 8, lines 5-17).

However, Raymond does not specifically indicate that the integration event should be duplicated to produce a methylotrophic yeast strain that comprises two copies of a human insulin precursor integrated into its genome.

The instant invention involves the integration of two separate constructs encoding a human insulin precursor into the genome of a host cell. *In re Harza* (274 F.2d 669, 124 USPQ 378 (CCPA 1960)) indicates that a "mere duplication of parts has no patentable significance unless a new and unexpected result is produced" (see for example MPEP § 2144.04 [R-1] (VI)(B)). In the instant case, the integration of a first and a second DNA construct comprising a human insulin precursor does not provide a new and unexpected result when compared to the same cell harboring only a first integrated construct; essentially, the instant invention is merely a duplication of parts, wherein the duplicated part is a construct comprising a human insulin precursor. Thus, the ordinary skilled artisan would recognize that it was obvious to integrate additionally copies of a gene into the genome of a host cell, and thus would be motivated to create a methylotrophic yeast strain comprising two genomic copies of a human insulin precursor. Absent evidence to the contrary, the skilled artisan would have had a reasonable expectation of success when duplicating the integration event taught by Raymond to create a methylotrophic yeast strain comprising two genomic copies of a human insulin precursor.

Claims 1, 3 and 2* and 5* are rejected under 35 U.S.C. 103(a) as being unpatentable over Raymond (as set forth above in the rejection of claims 1, 3, 5 and 24), in further view of EP 0195691 (see entire document).

Raymond teaches all of the elements set forth above in the rejection of claims 1, and 3. Briefly, the reference teaches a methylotrophic yeast strain comprising two constructs integrated into its genome, wherein the constructs encode a human insulin precursor. However, Raymond does not specifically teach the production of a human insulin precursor having the formula B(1-

30)-Y1-Y2-A(1-21), or the use of an export/secretion signal sequence (although Raymond clearly contemplates the usefulness of secreting their proteins-see for example column 4, lines 58-65). Note- * represents the claim rejected specifically by the new combination of references.

EP 0195691 teaches the construction of a human insulin precursor having the formula B-X-Y-A, where B represents the 30 amino acid long B polypeptide of insulin, X and Y both represent either lysine or arginine, and A represents the 21 amino acid A polypeptide of insulin (see for example the Abstract, constructs 7-10 in Table 1, page 2, lines 5 –7 and page 4, line 20 to page 5, line 7). This construct is identical to the B(1-30)-Y1-Y2-A(1-21) construct indicated in the instant claims. EP 0195691 teaches that these particular constructs have the distinct advantage of being easily converted into human insulin (see for example page 3, lines 28-31), and are produced in high yields when expressed in yeast cells (see for example page 4, lines 20-30). EP 0195691 further teaches the use of the yeast α-mating factor secretion signal as operably linked to the B(1-30)-Y1-Y2-A(1-21) insulin precursor, in order to improve the yield of the insulin precursor in the culture broth (see for example page 6, lines 1-12).

It would be obvious to produce the B(1-30)-Y1-Y2-A(1-21) insulin precursor taught by EP 0195691 using the methylotrophic yeast strains and methods taught by Raymond because both methods are directed to the same process: the production of an insulin precursor using yeast cells.. The ordinary skilled artisan would have been motivated to use the yeast strains and methods taught by Raymond for the production of insulin because, not only does Raymond teach their method is useful for the production of the pharmaceutically relevant protein, but also because EP 0195691 teaches that their particular insulin construct is both easily converted into the pharmaceutically relevant processed insulin and produced in large quantities in yeast cells.

Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when producing the B(1-30)-Y1-Y2-A(1-21) insulin precursor of EP 0195691 using the methylotrophic yeast strains and methods taught by Raymond.

Claims 1-3, 5 and 24* are rejected under 35 U.S.C. 103(a) as being unpatentable over Raymond and EP 0195691, in further view of Brierley (as recited above in the rejection of claims 1, 3 and 5 under 35 USC § 102) and Tully *et al.* (US 6,337,193; see entire document; henceforth Tully). Note- * represents the claim rejected specifically by the new combination of references.

Raymond and EP 0195691 teach all of the elements set forth above in the rejection of claims 1-3 and 5. Briefly, the combined references teach a methylotrophic yeast comprising two constructs integrated into its genome, wherein the constructs encode a human insulin precursor having the formula B(1-30)-Y1-Y2-A(1-21). However, Raymond and EP 0195691 do not specifically teach the use of the *HIS4* gene as a selectable marker on the first construct and the use of the zeocin-resistance marker as a selectable marker on the second construct.

Brierley teaches the construction of a methylotrophic yeast strain wherein the yeast comprises an expression construct for the recombinant production of a heterologous protein. A specific construct taught by Brierley comprises a promoter for a methanol responsive gene such as *AOX1* (see for example column 6, lines 37-65), operably linked to the *S. cerevisiae* α-mating factor (AMF) export signal as fused to a heterologous protein, and further operably linked to a transcriptional terminator such as the *AOX1* terminator (see for example column 4, lines 13-30). The constructs can also comprise a selectable marker gene such as *HIS4* or *ARG4* (see for

example column 7, lines 39-54). Brierley teaches that one or more (e.g., two) of these constructs can be integrated into the genome of the yeast at the same or different loci (see for example column 8, lines 5-32), and the skilled artisan would clearly recognize the need to use two constructs having two different selectable markers when selecting an integrant having multiple integrated copies.

Although Brierley does not specifically teach that the Zeocin resistance gene can also be used as a selectable marker, Tully teaches that the Zeocin resistance gene is interchangeable as a selectable marker with the *Pichia HIS4* and/or *ARG4* selectable markers (see for example column 7, lines 3-13) when producing heterologous proteins in methylotrophic yeasts (see for example the Abstract and column 2, lines 5-28). It would have been obvious to combine the teachings of Brierley and Tully because both teachings deal with the use of interchangeable selectable markers to introduce heterologous proteins into methylotrophic yeast strains for the purpose of their recombinant production. The ordinary skilled artisan would have been motivated to combine these teachings in order to make use of any particular selectable marker, where it was well known in the art at the time of filing that multiple selectable markers were interchangeable. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when using either the *HIS4*, *ARG4* or Zeocin resistance gene as a selectable marker when transforming methylotrophic yeast for production of a heterologous protein.

It would have been obvious for the ordinary skilled artisan to combine the teachings of Raymond and EP 0195691 with the combined teachings of Brierley and Tully (as set forth above as combinable with separate obviousness, motivation and expectation of success statements)

because all four teachings are concerned with the resolution of a similar problem (the recombinant production of a protein in yeast cells) using a similar methodology (the use of expression constructs for integration into a host cell genome, wherein the constructs comprises a promoter element, the *S. cerevisiae* α-MF secretion signal, a heterologous protein of interest (such as insulin), a terminator sequence, and a selectable marker), and are thus combinable for the purpose of solving a common problem. The ordinary skilled artisan would have been motivated to combine the teachings of Raymond and EP 0159691 with the combined teachings of Brierley and Tully in order to use the full complement of available selectable markers, which are well-known as being interchangeable. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when combining the teachings of Raymond and EP 0159691 with the combined teachings Brierley and Tully to use first and second constructs comprising the HIS4 and Zeocin selectable markers (respectively) because both markers are well-known to be functional in methylotrophic yeast.

Allowable Subject Matter

Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JAMES KETTER
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